REMARKS

Reconsideration is requested.

Claims 76-106, 109 and 111-114 are pending. Claims 76-105 and 112-114 have been withdrawn from consideration.

Claim 106 has been revised, without prejudice, to include the details of unamended claim 109. Claims 1-105, 107, 108, 110 and 112-114 have been canceled, without prejudice. Claims 115-118 have been added and support for same may be found throughout the specification. No new matter has been added.

Claims 106, 109, 111 and 115-118 will be pending upon entry of the present Amendment. The present Amendment does not add new claims without canceling at least a corresponding number of claims. The new and amended claims read on the elected subject matter. The present Amendment is not believed to raise new issues requiring further search and/or consideration.

The Examiner is requested to examine all of the recited species mutations of the claims as the elected species has been found to be allowable over the art of record. At a minimum, the Examiner is requested to examine all of the recited species as described on page 10 of the Office Action dated November 1, 2007 as the independent claim 106 is in condition for allowance upon entry of the present Amendment. Entry of the present Amendment and allowance of all of the claimed subject matter are requested.

The mutations of the revised claims are specifically described, for example, on pages 6 and 56-62 of the substitute specification filed July 11, 2008.

The Section 112, first paragraph "enablement", rejection of claims 106, 109 and 111, is obviated by the above amendments. Withdrawal of the rejection is requested in view of the above and the following comments.

The claims have been revised to refer to specifically disclosed mutations and the use of same in assessing putative anti-prostate cancer and anti-breast cancer agents.

The applicants have demonstrated in the specification the existence of the recited mutations in prostate and breast cancers. Moreover, the specification describes, for example, on pages 22 and 29 of the substitute specification filed July 11, 2008 that the disclosed mutations in plexinB1 nucleic acid and polypeptide sequences are associated with invasive cancers which are prone to metastasis. Further, the specification describes the following on page 31: "A decrease in activity [of the plexinB1 sequences containing the mutations of the invention] in the presence relative to the absence of test compound is indicative that the compound is a putative anti-cancer agent." Further, the Wong et al reference of record ("Plexin-B1 mutations in prostate cancer" PNAS, November 27, 2007, vol. 104, No. 48, 19040-9045) demonstrates that expression of mutant versions of the PlexinB1 gene increase the invasive capacity of the cells relative to wild type and vector controls (see page 19042, right column, last sentence of section titles **Mutation of Plexin-B1 Increases Cell Motility and Invasion**). Wong et al further confirm that the tested mutants have lost or have considerably reduced their ability to bind R-Ras and inactivate it.

> "Cells expressing mutant Plexin-B1 will therefore have an increased ratio of active/inactive R-Ras relative to cells expressing WT Plexin-B1. Activated R-Ras activates integrins resulting in an increase in cell adhesion and motility. The finding of a loss of R-RasGAP activity for mutant Plexin-B1 is therefore consistent with our *in vitro* assays." See page 19044, left column, first full paragraph of Wong et al.

Wong et al. conclude that

> "Overexpression of Plexin-B1 protein in primary prostate cancers was also seen. Together these results suggest that Plexin-B1 has a role in prostate cancer progression." See page 19044, left column, second full paragraph of Wong et al.

The applicants submit that it is "clear"[1] that expression of the Plexin-B1 sequence containing the A5653G mutation results in or is related to cancer progression and that identification of an agent which reduced expression of same according to the claims would be useful as a subject of further study as a putative anti-cancer agent, as claimed. One of ordinary skill in the art will be able to make and use the claimed invention without undue experimentation.

The claims do not require or relate to determining an increase in the wild-type Plexin-B1 to identify a putative anti-cancer agent. Clarification of the Examiner's

[1] "Thus, it is not clear if this mutation is a positive or negative regulator of prostate tumor or any tumor formation as the mutation appears to be associated with both positive and negative regulation of tumor formation and one of skill in the art would not predictably know what change in expression of the A5653G mutant B1 nucleic acid would be important for affecting tumor formation and would not predictably be able to identify and/or obtain a compound as a putative anti-cancer agent based on change in expression of the A5653G mutant plexinB1." See page 2 of the Office Action dated September 25, 2009.

criticisms in this regard is requested in the event the rejection is maintained based on same.[2]

The specification describes the claimed method of identifying a compound as a putative anti-prostate cancer or anti-breast cancer agent based on plexin-B1 sequences having specifically identified mutations. The finding of overlap in mutations found in breast and prostate cancers (i.e., positions 5059, 5069, 5458, 5452 and 5713) would reasonably suggest to one of ordinary skill in the art that testing of putative anti-cancer agents according to the claimed methods would identify anti-cancer agents useful in treating breast and prostate cancers. See Tables 1 and 2 of the specification and page 3 of the Office Action dated September 25, 2009[3]. The Examiner's general reference to a 1985 textbook (i.e., Taber's Cyclopedic Medical Dictionary[4]) is not believed to be sufficient to demonstrate the alleged unpredictability of the presently claimed invention and/or the level of ordinary skill in the art at the time of the present application (i.e., 2003). The applicants again note that the claims relate to identification of putative anti-cancer agents for prostate and breast cancer. The Examiner's comments on page 3 of

[2] "Additionally, it is not predictable that determining an increase in the wild-type plexinB 1would lead to the identification of a putative anti-cancer agent.... Thus, given that plexin B 1 is upregulated in ovarian and colorectal cancers, the determination of an increase in the wild-type plexin B 1 by a test compound would not predictably identify a putative anti-cancer agent. Thus, undue experimentation would be required for identifying and/or obtaining a putative anti-cancer agent by the claimed method." See page 3 of the Office Action dated September 25, 2009.

[3] "Furthermore, given that A5653G mutant plexin B1 has only be identified in prostate cancers, one of skill in the art would not predictable expect that agents that affect the expression of this mutant plexinB 1 nucleic acid would be putative anti-cancer agents for any cancer because it is well known in the art that cancers are heterogeneous in phenotype and genes expressed and cancer therapeutics are not predictably effective for all cancers."

[4] Id.

the Office Action dated September 25, 2009 relating to a variety of cancers are believed to be moot in view of the above.

Similarly, the Examiner's criticisms on page 4 of the Office Action dated September 25, 2009 of the recitation of the range of mutants recited in the unamended claims are believed to be moot in view of the above.

As for the Examiner's dismissal of the results present in Wong et al. as being based on *in vitro* studies on cell lines "which do not predictably extrapolate to *in vivo* anti-cancer activity", the Examiner is requested to see, for example, the indication in Wong et al. that standard *in vitro* methods of identifying oncogenes "have not been feasible because of an inability to maintain exogenous expression of Plexin-B1 over time and will require inducible vectors."[5] Wong et al. conclude however that "Plexin-B1 is likely to be a key player in cancer invasion and metastasis and is a potential target for anticancer therapy." One of ordinary skill in the art will believe that the results of Wong et al. may be predictably extrapolated to identify compounds as putative anti-prostate cancer or anti-breast cancer agents, as claimed.

The applicants further submit that the totality of the evidence in the specification and the art of record will be persuasive to one of skill in the art that the claimed plexin B1 mutations drive the development of and/or progression of cancer and that changes in the expression of mutant plexin B1 will affect cancer growth and progression.

The specification discloses mutations in plexin B1 which occur at high frequency in prostate and breast cancer. This is confirmed by Wong et al (of record). Mutations

found in cancer cells are discussed in Stratton MR et al. Nature 458: 719-724, 2009 (copy attached). In particular, Stratton et al describes the difference between passenger mutations, which are incidental mutations which are not related to cancer, and driver mutations, which provide a selective advantage to the cancer cells over normal cells and drive the development of and/or progression of cancer (see page 721 Box 1).

It is clear from Stratton et al that many point mutations which are found in cancer cells are passenger mutations. However, the data provided by the specification, which is supported by Wong et al, provides convincing evidence that all the mutations of the claims are not passenger mutations, but are in fact driver mutations that are causative of carcinogenesis or drive the progression of the disease.

The evidence that the claimed mutations are driver mutations can be summarised as follows.

1. The claimed mutations alter the amino acid sequence of the protein

2. The claimed mutations were independently confirmed using 2 methods

3. Many of the mutations were found in more than one cancer

4. The claimed mutations are somatic

5. The mutations were in a restricted region of the gene. The incidence of mutations in this region is 331 mutations/Mb DNA analyzed compared to 1.2 non-functional mutations/Mb in the cancer genome as a whole.

[5] See page 19044, left column of Wong et al.

6. The ratio of amino acid altering mutations to non-amino acid altering mutations (non-synonymous: synonymous ratio) was 73:1, compared to the 1:2 which would expected for chance passenger mutations

7. Five of the claimed mutations are in evolutionarily highly conserved regions

8. Plexin B1 is known to interact with many known cancer genes (e.g. ErbB2, c-Met).

9. All four mutations tested altered the in vitro function of the plexin B1 protein.

The totality of all of the evidence summarized above would convince a skilled person that the claimed mutations in plexin B1 drive the development and/or progression of cancer and therefore altered expression of mutant plexin B1 will alter cancer growth and development.

As for the predictability of extrapolating results from Wong et al. Stratton et al states at page 722 col 1;

> "Because cancer cells are dependent on the abnormal proteins encoded by mutated cancer genes, they have become targets for the development of new cancer therapeutics"

In other words, one or ordinary skill in the art would reasonably expect that mutated cancer genes and their products would be targets for anti-cancer drugs. This is confirmed on page 722 cols 1-2, which state;

> "Because many [point-mutated cancer genes] are kinases that are activated by the mutations found in cancer, they have prompted a wave of drug discovery to find inhibitors

> that may serve as anticancer therapeutics, some of which are already in clinical trial".

Point-mutated cancer genes are therefore well-known in the art to provide potential targets for new drugs for cancer treatment and the mutated plexin B1 sequences which are described in the specification would be reasonably expected to be potential targets for anticancer drugs.

The Examiner also alleged that the *in vitro* effects of the claimed mutations described in Wong et al cannot be extrapolated to *in vivo* anticancer activity.

However, those skilled in the art routinely infer a putative anti-cancer activity from *in vitro* testing. Cell lines are routinely used as part of the process for testing new drug. *In vivo* testing in animals only comes at a late stage in the development process, for reasons of cost and speed. The process of drug discovery demands a target - in this case mutated Plexin B1. A high throughput screen will then be devised to test thousands of agents against either the protein or using a cell-based assay (e.g., www.fluofarma.com). Confirmatory tests will then be undertaken in cell lines with a lead compound. If promising, then a lead compound identified as a putative anti-cancer agent through in vitro assays would be tested in animals.

This is confirmed by Zips et al (of record), which states on page 3 col 1

> Compared to animal tumor models, in vitro methods are less expensive and less time consuming, thereby allowing evaluation of large quantities of new anti-cancer agents. Molecular methods to prove and quantify the potential of several drugs to affect the molecular target...facilitate the selection of promising candidate drugs.

Zips et al also states on page 6 col 1;

> A step-wise procedure from in vitro to in vivo seems reasonable to reduce the large quantity of potential drugs to a few promising agents for further clinical testing.

The claimed invention is supported by an enabling disclosure.

Entry of the present Amendment and withdrawal of the Section 112, first paragraph "enablement", rejection are requested.

The Section 112, first paragraph "written description", rejection of claims 106, 109 and 11, and the new matter rejection or objection to the specification stated on pages 12-14 of the Office Action dated September 25, 2009, are obviated by the attached Declaration.

As discussed with the Examiner during a teleconference on or about November 19, 2009, the cited sections of Rule 57 are not applicable to the present application. The specification refers to the correct accession number. Neither the unamended nor amended claims refer to "the plexinB1 coding sequence of AB0007867.1" as asserted by the Examiner on page 11 of the Office Action dated September 25, 2009. The claims are supported by an adequate written description and the prior amendments to the specification did not introduce new matter. Withdrawal of the Section 112, first paragraph "written description", rejection and the new matter rejection or objection to the specification is requested. The Examiner is requested to contact the undersigned, preferably by telephone, in the event anything further is required in this regard.

The claims are submitted to be in condition for allowance. Entry of the present Amendment and a Notice of Allowance are requested.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: /B. J. Sadoff/
B. J. Sadoff
Reg. No. 36,663

BJS:pp
901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100